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(54) METHODS FOR IDENTIFYING COMPOUNDS WHICH MODULATE THE **ACTIVITY OF MSH5**

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Related U.S. Application Data

- (62) Division of application No. 09/469,636, filed on Dec. 22, 1999, now Pat. No. 6,444,873.
- (60) Provisional application No. 60/113,487, filed on Dec. 22, 1998.

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(56)References Cited

U.S. PATENT DOCUMENTS

5,972,621 A * 10/1999 Tartaglia et al. 6,333,153 B1 * 12/2001 Fishel et al.

FOREIGN PATENT DOCUMENTS

wo

WO 9901550

1/1999

OTHER PUBLICATIONS

"Antisense Nucleic Acids for Therapeutic and Other Applications", 1998, http://www.enzobio.com/therapeutics/antisense_primer.

Winand et al., "Cloning and characterization of the human and Caenorhabditis elegans homologs of the Saccharomyces cerevisae MSH5 gene", Genomics, Oct. 1998, 53(1):69-80.

Akiyama Y, et al. "Germ-line mutation of the hMSH6/GTBP gene in an atypical hereditary nonpolyposis colorectal cancer kindred". Cencer Res Sep. 15, 1997;57(18):3920-3.

Bawn S, et al. "A mutation in the MSHS gene results in alkylation tolerance." Cancer Res. Jul. 1, 1997;57(13):2715-20.

Baker SM, et al. "Involvement of mouse MIh1 in DNA mismatch repair of meiotic crossing over." Nat Genes, Jul. 1996;13(3):336-42.

Baker SM, et al. "Male mice defective in the DNA mismatch repair gene PMS2 exhibit abnormal chromosome synapsis in meiosis." Cell. Jul. 28, 1995;82(2):309-19.

de Vries, SS, et al. "Mouse MutS-like protein Mah5 is required for proper chromosome synapsis in male and female meiosis". Genes Den Mar. 1, 1999;13(5):523-31.

Edelmann W, et al. "Meiotic pachytene arrest in MLH1-deficient mice". Cell. Jun. 28, 1996;85(7):1125-34.

Hollingsworth NM, ct al. "MSH5, a novel MurS homolog, facilitates meiotic reciprocal recombination between homologs in Seccharomyces cerevisiae but not mismatch repair." Genes Dev Jul. 15, 1995;9(14):1728-39.

Kolodner R. "Biochemistry and genetics of eukaryotic mismatch repair". Genes Den Jun. 15, 1996;10(12):1433-42.

Leach FS, et al. "Mutations of a mutS homolog in hereditary nonpolyosis colorectal cancer*. Cell. Dec. 17, 1993;75(6):1215-25. Miyaki M, et al. "Germline mutation of MSH6 as the cause of hereditary nonpolyosis colorectal cancer." Nat. Genet. Nov. 1997;17(3):271-2.

Modrich P, et al. "Mismatch repair in replication fidelity, genetic recombination, and cancer biology". Annu. Rev. Blochem. 1996;65:101-33.

Moreadith RW, et al. "Gene targeting in embryonic stem cells: the now physiology and metabolism". J Mot Med. Mar. 1997;75(3):208-16.

Mullins, I., J et al. "Transgenesis in the Rat and Larger Mammals" J. Clin. Invest. 1996;98: a37-a40.

Papadopoulos N, et al. "Mutation of a mutL homolog in hereditary colon cancer." Science. Mar. 18, 1994;263(5153):1625-9.

Pochart P, et al. "Conserved properties between functionally distinct MutS homologs in yeast." J Biol Chem. Nov. 28, 1997;272(48):30345-9.

Reitmair AH, et al. "MSH2 deficient mice are viable and susceptible lo lymphoid tumours." Nat Genet. Scp. 1995;11(1):64-70.

Ross-Macdonald P, et al. "Mutation of a meiosis-specific MutS homolog decreases crossing over but not mismatch correction." Cell. Dec. 16, 1994;79(6):1069-80.

Scamark RF. "Progress and emerging problems in livestock transgenesis: a summary perspective". Reprod Fertil Dev. 1994;6(5):653-7.

Winand NJ, et al. "Cloning and characterization of the human and Coencrhabditis elegans homologs of the Saccharomycus cerevisiae MSH5 gene". Genomics. Oct. 1, 1998;53(1):69-80.

de Wind N, et al. "Inactivation of the mouse Mah2 gene results in mismatch repair deficiency, methylation tolerance, hyperrecombination, and predisposition to cancer. Cell. Jul. 28, 1995;82(2):321-30.

cited by examiner

Primary Examiner—Ruth A Davis (74) Attorney, Agent, or Firm—Drinker Biddle & Reath LLP

ABSTRACT

An animal, e.g., transgenic mouse, in which the MSH5 gene is misexpressed. The animal is useful for screening treatments for a number of conditions. Methods for identifying contraceptive agents are also described.

4 Claims, 8 Drawing Sheets



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(56) References Cited

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FOREIGN PATENT DOCUMENTS

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Baker SM, et al. "Male mice defective in the DNA mismatch repair gene PMS2 exhibit abnormal chromesome synapsis in mejosis." Cell. Inl. 28, 1995;82(2):309-19.

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Leach PS, et al. "Mutations of a mutS homolog in heroditary nonpolyosis colorectal cancer". Cell. Dec. 17, 1993;75(6):1215-25.

Miyaki M, et al. "Germlino mutation of MSH6 as the cause of hereditary aonpolyosis colorectal cancer." Nat. Genet. Nov. 1997;17(3):271-2.

Modrich P, et al. "Mismatch repair in replication fidelity, genetic recombination, and cancer biology". Annu. Rev. Biochem. 1996;65:101-33.

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Seamark RF. "Progress and emerging problems in livestock transgenesis: a summary perspective". Reprod Fertil Dev. 1994;6(5):653-7.

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